# POTENTIAL FOR INTENSITY MODULATED RADIATION THERAPY TO PERMIT DOSE ESCALATION FOR CANINE NASAL CANCER*

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**ABSTRACT**

We evaluated the impact of inverse planned intensity modulated radiation therapy (IMRT) on the dose-volume histograms (DVHs) and on the normal tissue complication probabilities (NTCPs) of brain and eyes in dogs with nasal tumors. Nine dogs with large, caudally located nasal tumors were planned using conventional techniques and inverse planned IMRT for a total prescribed dose of 52.5 Gy in 3.5 Gy fractions. The Equivalent Uniform Dose (EUD) for brain and eyes was calculated to estimate the Normal Tissue Complication Probability (NTCP) of these organs. The NTCP values as well as the DVHs were used to compare the treatment plans. The dose distribution in IMRT plans was more conformal than in conventional plans. The average dose delivered to one third of the brain was 10 Gy lower with the IMRT plan compared to conventional planning. The mean partial brain volume receiving 43.6 Gy or more was reduced by 25.6% with IMRT. As a consequence, the NTCPs were also significantly lower in the IMRT plans. The mean NTCP of brain was two times lower and at least one eye could be saved in all patients planed with IMRT. Another possibility with IMRT is dose escalation in the target to improve tumor control while keeping the NTCPs at the same level as for conventional planning.

## INTRODUCTION

Radiotherapy, alone or in combination with surgery, is standard treatment for canine nasal tumors and is usually given as external-beam megavoltage therapy (1-15). Despite various radiotherapy time-dose prescriptions, almost all dogs are ultimately euthanized due to tumor recurrence and local progression (16, 17). Perhaps a higher total dose of radiation would result in enhanced tumor control and increased survival. Unfortunately, dose escalation in the target is limited by the risk of complications in the surrounding normal tissues (18). For canine nasal tumors, the dose limiting tissues are the brain and the eyes (16, 17). Due to the extension of most tumors either into the cranial cavity or frontal sinus, normal brain is often included in the planning target volume (PTV).

The response of normal tissue to radiation is not only related to the dose-time parameters, but also to the partial volumes of normal tissue receiving variable dose levels (19, 20). Brain necrosis as well as blindness is a function of the irradiated partial volume. To increase the radiation dose to the target, the volume of brain and eye receiving radiation should be minimized. This goal can be accomplished by the application of more conformal radiation delivery.

In veterinary medicine, state of the art radiation therapy is conventional three-dimensional treatment using photons delivered through, rectangularly-shaped fields, possibly with additional blocking and wedges. Another treatment option is proton conformal radiotherapy which has been applied experimentally to canine nasal tumors (21). The degree of conformation could be improved with protons compared to conventional treatment. Hence, fewer normal tissue complications probabilities are expected when applying proton radiotherapy, but access to proton treatment machines is limited.

Another method to achieve dose conformation is intensity modulated radiotherapy (IMRT) (22, 23). In the mid-1990s computer-controlled multileaf collimators were developed that provided dynamic control of aperture sequence to spatially modulate the x-ray beam intensity. That technology has opened the door to IMRT, in which the delivery of radiation to the patient is performed via fields that have non-uniform photon fluence. The field is geometrically shaped and the intensity is varied pixel-by-pixel within the shaped field, therefore complex dose distributions can be produced to protect normal structures selectively allowing dose escalation in the target. The realization of this intensity modulation is performed with the use of an inverse treatment planning system where dose is specified and a computer determines the shape and dose-intensity of fields. In the treatment planning process dose constraints are set for both normal tissues and the PTV. Therefore IMRT seems to be relevant to canine nasal tumors where the brain and eyes are close to the tumor (24).

In this study, comparative planning, conventional versus inverse-planned IMRT was conducted for dogs affected by a nasal tumor. The goals were 1) to compare the differences in dose distribution to the brain and eyes, and 2) to estimate the risk of severe late effects in those normal tissues for a prescribed dose usually applied with conventional treatment. Additionally, a dose escalation simulation was performed using IMRT treatment planning to evaluate the ability of this technique to increase safely the radiation dose to the tumor. The practical realization of the planned intensities for the application of the IMRT plans was verified for one dog by absolute and relative dose measurement in a solid water phantom.

It should be noted that our study is a pure simulation and no treatment was performed.

## MATERIALS AND METHODS

Nine dogs with a caudally located nasal or paranasal tumor and substantial partial brain volume within the target were studied. Four dogs were of mixed breed, the remaining five dogs were one each of the following breeds: Standard Poodle, Weimaraner, Dachshund, Beagle, Giant schnauzer. The tumor was growing in the left side of the nose in six dogs and in the right side in three dogs.

Planning computed tomography (CT) was performed for each patient in the treatment position. Depending on the size of the patient, 2-6 mm continuous slices were acquired from the tip of the nose to the first cervical vertebra for treatment planning.

For immobilization, individual bite blocks and vacuum cushions placed into a plexiglas box were used. Lead marks were placed on anatomic landmarks, such as the medial canthus of one eye or the midline of the nasal planum at the muco-cutaneous junction. Another lead mark was placed onto the bite block. The CT data were transferred to the treatment planning system Eclipse (Version 7.2.35, Varian Medical Systems, Palo Alto, CA).

The PTV was defined in each CT slice. First, the gross tumor volume (GTV), which included the region of the visible tumor in the CT images, was outlined. Secondly, the clinical tumor volume (CTV) including the GTV and the region considered at risk for occult or microscopic disease was outlined. Fluid accumulation within the frontal sinuses was considered as region at risk and, therefore, included into the CTV. Lastly, a margin of 3 mm around the CTV was added in every dimension to account for setup errors and patient motion and specified as the planned target volume (PTV). Organs at risk, typically the eyes and brain, were also contoured, since they are dose limiting.

The selected dogs were planned simultaneously using conventional planning and inverse-planned IMRT. The photon energy used in the simulations was 6 MV. Heterogeneity correction was used in the dose calculation algorithm of all treatment plans. For the

conventional plans, a photon dose distribution was manually optimized using wedges and multileaf collimators. Several plans with different gantry angles and number of beams were evaluated and the optimal plan selected. In one dog, a treatment plan with three fields; and in the other 8 dogs two-field plans were used.

For IMRT- inverse treatment planning, 5 fields arranged around the PTV were used to minimize the dose to normal tissue. All fields were equally spaced at successive gantry angles of 72°. The inverse planning allowed defining upper and lower dose constraints, taking into account the tolerance of various critical normal tissues, and the dose desired in the CTV and PTV. The dose volume constraints were based on the available normal tissue data (20, 25) (Table 1). The tolerance data were adjusted to 3.5 Gy fractions using the linear quadratic model (26), with an $\alpha/\beta = 2$ for late responding normal tissue. A value for $\alpha/\beta = 4$ would increase the tolerance dose levels of about 10%. This uncertainty is acceptable considering that the tolerance data were obtained from human radiotherapy studies. The normal tissue constraints were reduced from their starting value during the optimisation procedure as long as dose constraints for the PTV were achieved.

In a first step the total prescribed dose for conventional and IMRT plans was 52.5 Gy in 3.5 Gy fractions given on a Monday, Tuesday, Thursday, Friday protocol, which is our standard prescription for canine nasal tumors. The prescribed dose was at the 100% isodose line. It was attempted to keep the dose variation in the PTV within +7% and -5% of the prescribed dose as recommended by the International Commission on Radiation Units and Measurements (ICRU) (27). In a second step the target- dose was escalated to 59.5 Gy for the IMRT plans.

We hypothesised that dogs with a complex PTV would benefit more from IMRT. Therefore, the ratio between the partial surface and the partial volume of the brain which was not part of the PTV was calculated and was used as a simple approach to evaluate the complexity of the

interface between PTV and brain. It is assumed here that when the surface of an object is increased by keeping the volume constant the complexity of the object is increased. The higher the surface-volume-ratio, the higher the complexity. The optimised intensities were transformed into the actual photon fluence using the leaflet motion calculation tool of Eclipse for dynamic MLC delivery. Dose distributions were always calculated using the actual fluences.

The computed treatment plan for one patient was verified in a solid water phantom. . Absolute dose was measured with a farmer ionization chamber at the isocenter. A two-dimensional dose measurement using a film was performed in a dorsal plane through the isocenter. The two-dimensional measurement was normalized in the isocenter to the absolute measurement and compared to the calculated dose distribution using a gamma analysis (28). Frequently the evaluation of a treatment plan and the comparison of different plans are based on visual evaluation of dose distributions on some selected CT slices. In addition, the dose volume histogram (DVH) for target and normal tissues may be compared. This process is often subjective, and estimation of cure and complication are qualitative. To avoid the subjective nature of comparing treatment planning based on physical dose we used estimates of normal tissue side effects. The treatment complications depend not only on the dose but also on the volume of the organ irradiated (19, 20). The calculation of the normal tissue complication probability (NTCP) from a 3D dose distribution is therefore divided into three independent steps; (1) conversion of the dose distribution into a DVH of the organ at risk, (2) reduction of the DVH to a single number and (3) conversion of this single number into NTCP. Dose volume histograms were calculated for the PTV, the brain and the eyes for both treatment techniques and all patients. A published DVH reduction scheme (29) was used and is based on the empirical power-law relationship between volume and dose. The original DVH is converted into a DVH where the whole organ volume corresponds to an Equivalent

Uniform Dose (EUD). Hence, the organ uniformly irradiated with EUD would result in the same radiation effect as the inhomogeneously irradiated tissue.

$$EUD = \left[ \sum_i D_i^{\frac{1}{n}} . V_i / V_{tot} \right]^n \qquad \text{(Eq. 1)}$$

where $V_i$ is the partial volume irradiated with dose $D_i$ in bin number i; $V_{tot}$ the whole organ volume; *n* is a volume exponent which depends on the organ and the end-point. The organ specific parameter n was taken from empirical human data (30). The formal equation giving NTCP when an organ is irradiated uniformly to EUD (19) is sometimes called the integrated normal model (31). The following equation describes the interrelation between *NTCP*, *EUD* and total volume $V_{tot}$.

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \qquad \text{(Eq. 2)}$$

with *x* a free variable and

$$t = [EUD - TD_{50}(V_{tot})] / [mTD_{50}(V_{tot})] \quad \text{(Eq. 3)}$$

where $TD_{50}$ is the tolerance dose which results in a 50% complication probability for some specified complication or end-point; appropriate to irradiating *all* the volume $V_{tot}$; and *m* defines the steepness of the curve.

In this publication, we relied on model parameters (n, m, TD50) compiled for humans (30), because we felt there were insufficient data on dose-volume relationships available for canine brain and eyes for the end points necrosis and blindness, respectively. The fit parameters for eyes and brain are listed in Table 2. The data are based on 2 Gy fractions and were adjusted to 3.5 Gy fractions used in our protocol by applying the linear quadratic model (26).

It should be noted here that the calculated NTCPs are only estimates of the clinically observed complication probabilities and subject to a large error. However, the NTCP values can be confidently used to compare different planning techniques.

## RESULTS

The total brain volume ranged from 55.6 to 99.1 $cm^3$ (mean 79.2 $cm^3$). The size of the PTV varied from 66.3 to 338.6 $cm^3$ (mean 176.8 $cm^3$) and was largest in dogs were the tumor involved a larger portion of the nasal cavity and paranasal sinuses. The partial brain volume within the PTV ranged from 8.3 to 16.1 $cm^3$ (mean 11.7 $cm^3$). The mean dose applied to one third of brain was approximately 10 Gy less with IMRT planning. The doses were always lower than 43.6 Gy (dose constraint for one third of the brain) with IMRT plans and higher than 43.6 Gy in dog 2 and dog 3 with conventional planning (Table 3).

According to the dose constraints used for IMRT planning, analysis of the DVHs indicated that, as expected, the conventional plans always involved a larger partial brain volume for the 63%, 70% and 83% isodose lines compared to the IMRT plans (Table 4). While 26.6% of mean relative partial brain volume would be included in the 83 % isodose ($\geq$ 43.6 Gy) with conventional planning, only 19.8 % would be included with IMRT. This represented a 25.6% reduction of relative partial brain volume exposed to 43.6 Gy. Comparison between conventional and IMRT dose distributions through the target volume and the brain, respectively, is illustrated in Figure 1. More brain tissue could be spared with IMRT. Obviously the NTCP increases with the irradiated partial brain volume. For all dogs, the NTCP for brain necrosis resulting from IMRT planning was lower compared to conventional planning (Table 5). The mean NTCP calculated from the conventional plans was twofold higher than the mean NTCP with IMRT plans.

For IMRT planning, a dose escalation from 52.5 to 59.5 Gy was performed and the NTCP values for brain and eyes were calculated. The prescribed dose of 59.5 Gy was chosen on the basis that the NTCP values for the brain only at that dose should be comparable to the NTCP values obtained with conventional planning for a prescribed dose of 52.5 Gy. The corresponding brain-NTCPs resulting from IMRT planning (59.5 Gy) was 27.6 ± 9.8% versus 20.3 ± 10.5% with conventional planning to a prescription of 52.5 Gy (Table 5). Patients with complex volume arrangements benefited more from IMRT than other patients. This is illustrated in Figure 2, where the ratio between NTCP(IMRT) and NTCP(conventional) was plotted as a function of the volume-complexity-parameter. The calculations were done for 52.5 Gy. If complexity increases the patients benefited more from IMRT.

Concerning the results of the eye on the side of the tumor, the NTCPs (52.5 Gy) were lower for IMRT planning as compared to conventional planning, however, since this eye is usually part of the PTV, the NTCPs cannot be improved significantly with IMRT (Table 5).

Looking at the dose escalation, the mean NTCP value with IMRT (59.5 Gy) was similar to the value obtained for conventional planning (52.5 Gy).

For the evaluation of the NTCPs of the eyes, we did not distinguish between the left and right eye. Since the applied dose is given to the tumor location we distinguished between the eye located close to the tumor, versus the eye located away from the tumor. This was then termed “non-tumor side”. The NTCPs (52.5 Gy) of the eyes at the non-tumor side were significantly lower for IMRT planning as compared to conventional planning (Table 5). These results indicated a better conformation of the dose to the PTV with inverse IMRT sparing the eye at the non-tumor side. The mean NTCP value obtained with IMRT at a prescription of 59.5 Gy was again similar to the one obtained with IMRT at a prescription of 52.5 Gy. Therefore, the eye at the non-tumor side can be spared as well when the dose is escalated.

Comparison between conventional and IMRT plans through the target volume and the eyes, respectively are illustrated in Figures 3. More eye tissue could be spared with IMRT
Based on phantom measurements, the absolute dose at the isocenter for was 0.4% smaller than the planned IMRT dose. Figure 4 shows the planned isodoses and the measured isodose as the lines in an absolute two-dimensional comparison. In Figure 4 also, measured and calculated dose distributions are compared using gamma-analysis (28) with a dose limit of 3% and a spatial limit of 3 mm. Areas where the dose difference exceeds the gamma criterion are shown in red. Ninety-eight percent of the dose area fullfilled the 3%/3mm-gamma criterion.

## DISCUSSION

When radiotherapy is used alone for treatment of canine nasal tumors, better tumor control can possibly be achieved by increasing the target dose while sparing the normal surrounding tissues. A boost radiation technique to increase local control has been assessed (18). The total dose was 57 Gy given in 3 Gy fractions in an overall time of 21 days. The dogs were given two fractions per day on 3 occasions during the first half of radiation therapy. Unfortunately, this technique resulted in unacceptable acute reactions. However, there may still be justification in trying to identify a way to deliver a higher dose to the PTV.
There are situations in which conventional planning cannot produce a satisfactory dose distribution because of the complex target geometry or the close proximity of sensitive normal tissues to the target. In the treatment of nasal and paranasal tumors, the dose limiting organs are brain and eye. In this study we evaluated the impact of IMRT on the dose to the brain and the eyes in dogs with nasal and paranasal tumors.
The rate of normal complications after radiotherapy is dose dependent, but for a given dose the probability of complications depends critically on the volume of irradiated normal tissue.

IMRT does not only have a positive effect on late, but also on acute normal tissue reactions. This is of particular importance in the treatment of nasal tumors, as acutely responding tissues may be dose limiting (5, 18).

In humans, IMRT is a relatively new development with everything important concerning this technique happening in the last 15 years. In the meantime improvements in clinical outcome have been achieved while minimizing the side effects that would have been expected with alternative conformal techniques. Examples include spinal cord dysfunction and xerostomia in head and neck cancers and damage to the bladder and rectum in prostate cancers (32).

Our data demonstrate the potential of IMRT for canine nasal tumors. With respect to the chosen complication endpoints, IMRT was superior to conventional planning. The NTCPs for brain were always smaller for IMRT plans as compared to conventional plans. Due to the better dose conformation with IMRT the prescribed dose was escalated from 52.5 Gy to 59.5 Gy. The dose of 59.5 Gy was chosen on the basis that the corresponding NTCP values were similar to those at 52.5 Gy with conventional planning. We found that it should be possible with IMRT to increase the dose to the PTV without increasing normal tissue complications in the brain. However, the clinical benefit for the patients in terms of tumor control is not known for a prescribed dose of 59.5 Gy or larger.

The smaller NTCPs obtained for the eyes indicated similarly a better conformation of the dose to the target with IMRT. Since in clinical routine a complication probability of typically 5% is accepted, IMRT could offer the possibility to save at least one eye in contrast to conventional treatments. Even though NTCP models have not been clinically validated, and thus the absolute value of the predictions may not be applicable, the relative NTCP comparisons should still be meaningful and relevant.

## CONCLUSION

IMRT with inverse treatment planning has the potential to improve radiotherapy of nasal and paranasal tumors in dogs by reducing normal tissue dose and allowing radiation dose escalation to the PTV. This advantage could be seen especially when treating complex shaped targets.

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**TABLES**

Table 1: Dose Constraints of Planning Target Volume (PTV), Brain (20) and Eye (25) for IMRT-Inverse Treatment Plans. Total Prescribed Dose 52.5 Gy. The Dose Constraints taken from the literature for 2 Gy fractions (third column) were converted to 3.5 Gy fractions for our simulation (fourth column).

| Structure / Organ | Volume [%] | Dose constraints [Gy] | |
|---|---|---|---|
| | | 2 Gy | 3.5 Gy |
| PTV | 0 | | < 56.2 (107%) |
| | 100 | | > 49.9 (95%) |
| Brain | 33 % | < 60.0 | < 43.6 |
| | 66 % | < 50.0 | < 36.4 |
| | 100 % | < 45.0 | < 32.7 |
| Globe right / left | 0 | < 54.0 | < 39.3 |
| Globe right / left | 50 % | < 35.0 | < 25.4 |

Table 2: Fit Parameter n /m /TD50 (converted for our Analysis for 3.5 Gy fractions) /End Point for Brain and Retina.

| Whole organ | n* | m** | TD50(2 Gy)/TD50(3.5 Gy) *** | End point |
|---|---|---|---|---|
| Brain | 0.25 | 0.15 | 60 / 43.62 | Necrosis |
| Retina | 0.2 | 0.19 | 65 / 47.27 | Blindness |

* volume exponent, depends on the organ and the end point.

** steepness of the curve between NTCP, EUD and $V_{tot}$.

*** tolerance dose, results in a 50% complication probability for specified end-point.

Table 3: Total Brain Volume, Planning Target Volume (PTV), Partial Brain Volume within PTV. Brain Dose-Volume Analysis for one third of the Brain comparing IMRT and 3D-RT Treatment Plans, prescribed dose 52.5 Gy.

| Patient Nr. | Total brain volume ($cm^3$) | PTV ($cm^3$) | Partial brain volume within PTV ($cm^3$) | Dose (Gy) to 1/3 volume of brain, prescribed dose 52.5 Gy | |
|---|---|---|---|---|---|
| | | | | Conventional | IMRT |
| Mean | 79.2 | 176.8 | 11.7 | 33.1 | 23.7 |
| SD* | 17 | 89.6 | 1.9 | 11.8 | 8.9 |

* standard deviation

Table 4: Brain Dose-Volume comparing IMRT and Conventional Treatment Plans for the 63%, 70%, 83% isodose lines (corresponding to the dose constraints used for IMRT-inverse treatment planning), prescribed dose 52.5 Gy.

| | Partial brain (%) volume in 63% isodose, receiving 32.7 Gy or more | | Partial brain (%) volume in 70% isodose, receiving 36.4 Gy or more | | Partial brain (%) volume in 83% isodose, receiving 43.6 Gy or more | |
|---|---|---|---|---|---|---|
| Patient Nr. | Conventional | IMRT | Conventional | IMRT | Conventional | IMRT |
| Mean | 36.3 | 27.2 | 32.3 | 23.5 | 26.6 | 19.8 |
| SD* | 9.6 | 5.2 | 8.6 | 3.7 | 6.9 | 4.8 |

* standard deviation

Table 5: Estimated Normal Tissue Complication Probability (NTCP) for Brain Necrosis and Eye Blindness Comparing the conventional and IMRT Treatment Plans. Calculation for 52.5 Gy prescribed dose and 59.5 Gy dose escalation.

| | NTCP (%) for brain necrosis | | | NTCP (%) of eye at tumor side for blindness | | | NTCP (%) of eye at non-tumor side for blindness | | |
|---|---|---|---|---|---|---|---|---|---|
| | 3D-RT | IMRT | | 3D-RT | IMRT | | 3D-RT | IMRT | |
| Patient Nr. | 52.5 Gy | 52.5 Gy | 59.5 Gy | 52.5 Gy | 52.5 Gy | 59.5 Gy | 52.5 Gy | 52.5 Gy | 59.5 Gy |
| Mean | 20.3 | 9.6 | 27.6 | 69.3 | 34.3 | 67.4 | 23 | 2.5 | 3.2 |
| SD* | 10.5 | 3.9 | 9.8 | 7.9 | 22.5 | 27.1 | 28.5 | 1 | 1.2 |

* standard deviation

**FIGURES**

Figure 1: Dorsal (rostral at top, left to reader's right) CT image with dose distribution for conventional radiation therapy (A) and intensity Modulated Radiation Therapy (IMRT) (B) at the same level. The colour-wash represents the 43.6-49.9 Gy isodoses (43.6 Gy and 49.9 Gy correspond respectively to the TD50 of the brain and to 95% of the prescribed dose). Dose distribution is more conformal to the planning treatment volume (red line), and sparing of brain (yellow line) is improved, using IMRT.

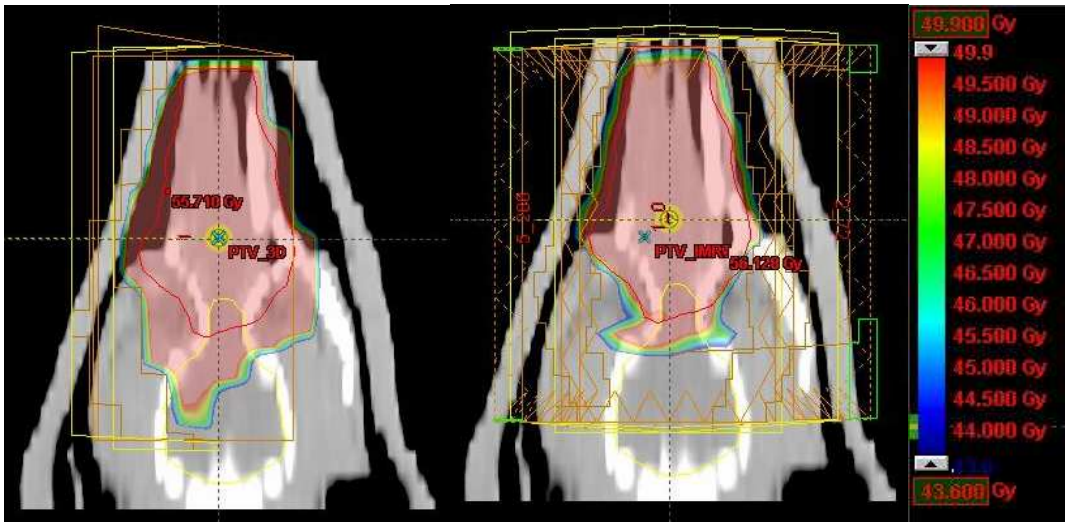

Figure 2: Estimated NTCPs (Normal Tissue Complication Probability) ratio comparing the conventional and Intensity Modulated Radiation Therapy (IMRT) plans as a function of the volume-complexity parameter. If the complexity increases the dogs benefit more from IMRT.

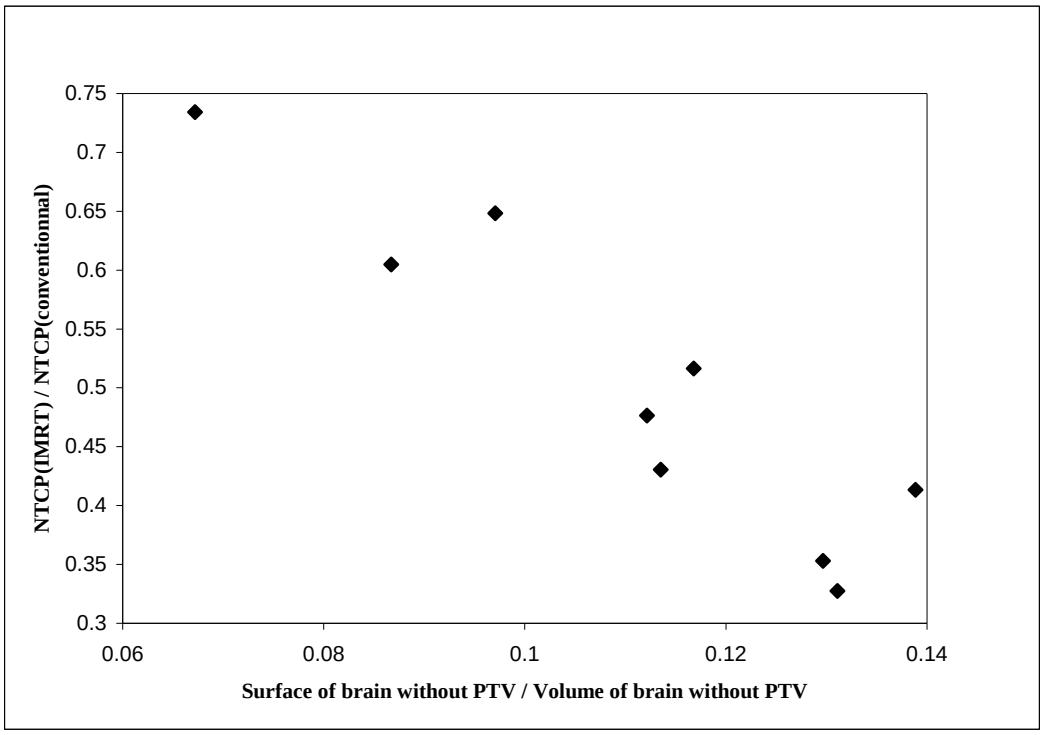

Figure 3: Transverse (dorsal at top, left to reader's right) dose distribution for conventional (A) and Intensity Modulated Radiation Therapy (IMRT) (B) at the level of the caudal aspects of the paranasal sinuses. The colour-wash represents the 39.3-49.9 Gy isodoses (39.3 Gy and 49.9 Gy correspond respectively to the dose constraint of the whole globe and to 95% of the prescribed dose). Dose distribution is more conformal to the planning treatment volume (red line), and sparing of eyes (blue line) is improved, using IMRT.

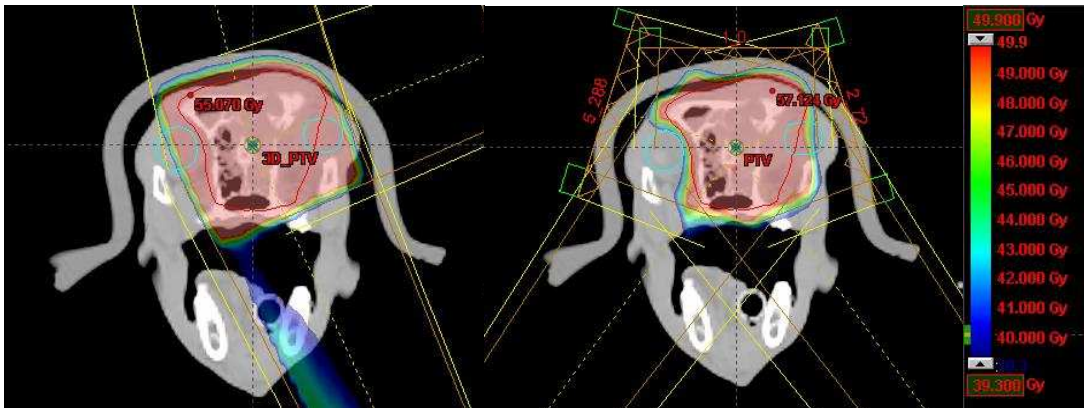


Figure 4: Dorsal plane, rostral at top, left to reader's left, of a dog planned with Intensity Modulated Radiation Therapy (IMRT). Absolute dose measurement (A) in the isocenter. Measured and calculated dose distribution comparison using Gamma-Analysis (B), red areas represent the dose difference which exceed the 3%/3mm-Gamma criterion.